

# The diagnostic value of indeterminate lung lesions on staging chest computed tomographies in patients with colorectal cancer

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## ABSTRACT

**INTRODUCTION:** Selection of pulmonary staging modality in colorectal cancer surgery is controversial. Computed tomography (CT) clearly outperforms x-ray in terms of sensitivity, but findings of indeterminate lung lesions remain a problem. The aim of the present study was to evaluate the significance of such indeterminate lung findings in staging CT scans.

**METHODS:** The study comprises a retrospective analysis of 131 consecutive patients who underwent colorectal cancer surgery in 2004. A preoperative staging CT scan of the chest and abdomen was performed in all patients. Twenty-six patients (20%) had indeterminate lung findings. Four died postoperatively. The remaining 22 were followed for a median period of 26 months.

**RESULTS:** In eight of the 22 patients (36%) lesions progressed. In one patient, the lesion turned out to be a primary lung cancer, in another a lymphoma. In the last six patients (27%), the lesions developed into colorectal cancer lung metastases within a median period of 15 months. These results were significantly different from those obtained in patients who had a normal CT, among whom only 6% developed lung malignancies in the follow-up period ( $p < 0.0001$ ). The development of lung metastases was significantly related to positive nodal status at operation and elevated carcinoembryonic antigen (CEA) level at follow-up ( $p < 0.05$ ).

**CONCLUSION:** Approximately one quarter of the indeterminate lung lesions found on staging CT in colorectal cancer patients developed into metastases and one tenth into other lung malignancies, which were most often diagnosed in the second year after surgery. The development of lung metastases was significantly related to positive nodal disease and postoperative CEA elevation.

The most common localisation of extrahepatic colorectal cancer (CRC) metastases is the lungs (5-10%) [1], but CRC without liver metastases is rare (2%) [2]. Selection of staging modality for determination of lung lesions has been controversial. Previous studies have reported a low sensitivity of chest x-ray as a routine staging modality (33%) in contrast to chest computed tomography (CT)

[3], which outperforms chest x-ray with reported sensitivities reaching 73% [4]. However, chest CT seems to have less specificity, and findings of indeterminate lung lesions therefore remain a problem. Some authors advise against the use of routine chest CT for staging purposes because of the uncertainty that lies in interpreting the significance of indeterminate lesions, because they most likely turn out to be benign and because the use of this modality would involve an unnecessary risk of worrying the patient [5].

The aim of the present study was to evaluate the significance of indeterminate lung findings in routine CT scans for staging of patients with CRC.

## METHODS

A retrospective analysis was made of the records of 131 consecutive patients who underwent surgical treatment for CRC in 2004 at the Department of Colorectal Surgery, Hillerød University Hospital. A preoperative, staging CT scan of the chest and abdomen was performed in all patients. Their cancer-related events were registered during a three-year period from 2004 up to 2007. Age, sex, pre- and postoperative CT and carcinoembryonic antigen (CEA) findings were registered, as were tumour location (rectum versus colon), pathology (tumour node metastasis (TNM) status), length of follow-up, and time and location of verified recurrence.

The patients were scanned with a single slice helical scanner (General Electric high-speed CT/i). The slice thickness was 1-10 mm and intravenous contrast was used in all cases. All CT scans were described by expert radiologists. Based on their diagnosis, the patients were grouped into: 1) normal chest CT, 2) manifest lung metastases, 3) suspected malignant lesions, and 4) indeterminate or tentatively benign lesions (Figure 1), e.g. fibrotic strand, pleural reaction, calcified nodule etc. These diagnoses were based on the subjective evaluation of at least two experienced radiologists at the time of the examination and not on an exact retrospective grading, as used – among others – by Kronawitter et al [5].

At the time of the CRC diagnosis, 89 of the 131 pa-

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 FIGURE 1

Indeterminate lung lesion marked with arrow.



tients (68%, 95% confidence limits: 60-76) had a normal chest CT, five (4%, 95% confidence limits: 1-9) had manifest lung metastases, 11 (8%, 95% confidence limits: 4-15) had suspected malignant lesions, and, finally, 26 (20%, 95% confidence limits: 14-28) had indeterminate or tentatively benign lesions.

The size of these indeterminate chest CT lesions was median 1.1 cm (range: 0.2-3.8 cm). Thirteen patients had a single lesion and seven had more than one lesion (median: 2, range: 2-3).

Four of the 26 patients with indeterminate or tentatively benign lesions on chest CT died postoperatively: two due to postoperative complications and the two others a few months after the operation due to concomitant chronic diseases (one from nephropathia and one from chronic lymphatic leukaemia). The remaining 22 patients were followed for a median of 26 months (range: 3-42 months).

All patients underwent surgery without delay. Further treatment and follow-up were decided at the weekly conference meetings of the Multidisciplinary Colorectal Cancer Team. All patients attended follow-up at least annually, or more frequently if necessary. Follow-up included abdominal and chest CT scan and CEA level determination. Positron electron microscopy (PET) scan was used in selected cases.

Patients with stage III colon cancer had adjuvant treatment with the FOLFOX4 regimen (oxaliplatin, leucovorin and 5-fluorouracil).

#### STATISTICAL ANALYSIS

Nonparametric statistics were used, including  $\chi^2$ -test,

Mann-Whitney test, Kaplan-Meier analysis and log rank test. The level of significance was 5%.

#### RESULTS

In eight of the 22 surviving patients with indeterminate or tentatively benign lesions, the lesions progressed in size and/or number (36 percent, 95% confidence limits: 17-59). Thus, six of the patients developed multiple lesions. Only in one patient with a primary lesion (diameter: 3.8 cm), probably a hamartoma, the lesion did not increase in size, but other malignant lesions developed in the follow-up period. Biopsies were drawn from two patients to ascertain the nature of the lesions. In one patient, the biopsy showed a primary lung cancer, which was detected on chest CT 15 months postoperatively. The other patient had a lymphoma diagnosed three months postoperatively. In the last six patients (27%, 95% confidence limits: 11-50), the lesions were clearly CRC lung metastases and they were detected within a median period of 15 months postoperatively (range: 5-31 months).

**Table 1** shows the characteristics of the patients with indeterminate lesions who developed CRC lung metastases compared with those who did not. All the former patients had nodal metastases at operation (N1 or N2 status) and significantly increased CEA levels at the latest follow-up visit. Only one of the patients had


 TABLE 1

Characteristics of six patients with indeterminate lung lesions who developed lung metastases compared with the 14 patients who did not.

Characteristic	+ lung metastases (n = 6)	- lung metastases (n = 14)	p-value
Age, years, median (range)	76 (56-81)	72 (55-90)	0.7
Sex (female/male)	4/2	4/10	0.2
T status			0.4
T1	0	1	
T2	0	1	
T3	5	12	
T4	1	0	
N status			0.047*
N0	0	8	
N1	3	4	
N2	3	2	
M status			0.2
M0	4	14	
M1	1	0	
Rectum	5	6	0.2
Colon	1	8	
Preoperative CEA, median, (range)	5.1 (2.2-115)	2.9 (0.5-29)	0.2
CEA at last follow-up, median, (range)	47.9 (7.2-127.0)	2.9 (0.5-683)	0.02*

CEA = carcinoembryonic antigen. \*) Statistically significant difference.

synchronous liver metastases at primary staging (17%, 95% confidence limits: 1-64).

Another two patients had developed liver metastases and one had a local recurrence at the time of development of CRC lung metastases. All were treated with chemotherapy for their disseminated disease.

In the other group with initial, normal-stage chest CT, five of the surviving 84 patients (6%, 95% confidence limits: 2-13) developed lung malignancies. All had T3 tumours, while three had N0 stage, one had N1 and one N2 stage. One patient turned out to have a primary lung cancer, while four patients (5%, 95% confidence limits: 1-12) developed lung metastases from their CRC. Thus, significantly more patients with indeterminate lung lesions on CT than patients without such indeterminate lesions developed lung malignancies (5/84 versus 8/22; log rank test,  $p < 0.0001$ ) and CRC lung metastases (4/84 versus 6/22; log rank test,  $p < 0.001$ ).

## DISCUSSION

The present study showed that about one quarter of the CRC patients in whom indeterminate lung lesions were found on preoperative chest CT later developed lung metastases. This incidence of later lung metastases was significantly higher in this group than in patients with normal CT findings (5% versus 27%,  $p < 0.001$ ). The lesions most often became manifestly malignant in the beginning of the second year after operation. This was also the case in patients in whom the indeterminate lung findings represented other malignancies (primary lung cancer and lymphoma), which was seen in 9% of the cases.

All patients with indeterminate lung lesions who developed lung metastases in the follow-up period had nodal disease (N1 or N2), which is in accordance with the findings of Brent et al [6]. No other significant differences in the characteristics of the patients were found except that the patient who developed metastases also had an elevated postoperative CEA level. Synchronous liver metastases were seen in only 17% of these patients.

Two or more expert radiologists subjectively assessed the routine chest CTs and reported that 20% of lung lesions were indeterminate among patients in the present study. In comparison, Kronawitter et al found 30% (low-likelihood of metastatic disease 10%, intermediate probability of metastatic disease 20%) [5], and McIntosh et al 24% [1]. These differences are probably rooted in the fact that the results depend much on the observer and the definition of "indeterminate". Moreover, the lack of consensus on a definition of indeterminate lung lesion hampers comparison of different studies. Thus, Kronawitter et al have proposed a set of categories for indeterminate lesions based on

their morphology [5], whereas Zerhouni et al proposed another set based on the critical density of the nodules [7]. We may also look to this distinction in search for an explanation for the finding of the present study: 36% of the patients with indeterminate lung lesions developed lung malignancies of which the majority were CRC metastases; Kronawitter et al, however, found that only 10% were CRC metastases [5], and in Brent et al the corresponding result was 17% [6]. Our finding of a high incidence of malignant development of the indeterminate lung lesions could also be ascribed to the long follow-up period used, as the malignant development often first seems to become manifest in the second year after surgery.

The present study did not find the incidence of lung metastases development in patients with rectal cancer to be significantly increased, which contrasts with the results reported by Valls et al [2] who found that more patients with rectal cancer than with colon cancer developed lung metastases without liver metastases.

Not surprisingly, an elevated level of the tumour marker CEA seems to predict malignant development of indeterminate lung lesions. Significantly higher follow-up CEA levels were seen in patients with indeterminate lesions that developed into lung metastases than among other patients, although in some of these patients the increased CEA level could be explained by concomitant dissemination to liver or local recurrence, which was seen in half of the patients.

As surgery is the only curative treatment for pulmonary (and hepatic) metastases from CRC [8], it is important to detect such metastases as early as possible. Fortunately, surgical treatment of CRC metastases has evolved considerably over the last two decades, and recent studies show promising survival rates after surgery with a curative intent in hepatic and lung metastases [9-11]. Furthermore, in patients with unresectable lung metastases, radiofrequency ablation can be performed with a good outcome [12].

The results of the present study indicate that a close follow-up with repeated CT scans is advisable in colorectal cancer patients with indeterminate lung lesions as determined by preoperative CT with a view to early detection of lung malignancies – especially in patients with nodal disease and postoperatively elevated CEA levels. This approach does, of course, invite the risk of inducing a new cancer by increased radiation exposure. However, this risk is found to be low [13] and should be weighed against the risk of death due to late diagnosis of CRC dissemination.

The retrospective design of the present study limits its strength as does the small number of patients. Large prospective studies of the significance of indeterminate lung lesions on preoperative CT scans are therefore

needed. Even so, the results indicate that intensive post-operative follow-up is important in these patients.

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